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EXAMINER

WILSON, M

ART UNIT

PAPER NUMBER

1633

DATE MAILED:

04/03/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.  
**09/197,056**

Applicant(s)

**Russell et al.**

Examiner  
**Wilson, Micha I C.**

Group Art Unit  
**1633**



☒ Responsive to communication(s) filed on Feb 16, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) 1-18 is/are pending in the application

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-18 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☒ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 and 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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### DETAILED ACTION

Applicant's arguments filed 2-16-00, paper number 7, have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The Information Disclosure Statements filed 8-21-99, paper number 5, and 9-2-99, paper number 6, have been considered and made of record.

Claims 1-18 are under consideration in the instant application.

### *Claim Rejections - 35 USC § 112*

1. Claims 1-18 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating the expression of a nucleic acid sequence encoding an immunogenic peptide *in vitro* comprising a) transfecting a cell with a nucleic acid sequence encoding an immunogenic peptide operably linked to a tetracycline regulatable system and b) regulating the expression of the sequence by administering tetracycline which results in an alteration in expression of the nucleic acid sequence, does not reasonably provide enablement for a method of regulating the expression of a nucleic acid sequence using a non-tetracycline regulatable system, or regulating the nucleic acid *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

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For clarification, the examiner considers an immunogenic polypeptide as any protein which induces an immune response such as GM-CSF or a chimeric T-cell receptor as disclosed in the specification (page 7, line 24).

### **Therapy**

Therapeutic and anti-tumor embodiments as in claims 11-12 are not enabled. At the time of filing it was unpredictable what vector, promoter, gene of interest, level of gene expression, target tissue, dosage or route of administration were required to obtain any therapeutic effect using gene therapy (Ross et al. of record, Sept. 10, 1996, Human Gene Therapy, Vol. 7, page 1781-1790; page 1786, column 1, paragraph 2; page 1786, column 1, paragraph 2; Verma et al. of record, Sept. 18, 1997, Nature, Vol. 389, pages 239-242; see page 239, 3rd column, line 10; page 239, column 1, line 16). It was not within the realm of routine experimentation for one of skill in the art to determine the parameters required to obtain any therapeutic or anti-tumor effect using gene therapy. The specification demonstrates constructing regulatable vectors encoding GM-CSF and a chimeric T-cell receptor. Applicants also demonstrate the chimeric T-cell receptor is capable of inducing IL-2 production in cells *in vitro* (page 29). Applicants do not teach the route of administration, vector, promoter or dosage that provides efficient gene delivery or the level of expression of GM-CSF or chimeric TCR required to obtain a therapeutic or anti-tumor effect. Nor do applicants demonstrate obtaining a therapeutic or anti-tumor effect using the method of the instant invention.

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Applicants point out that one patient had a clinical response using gene therapy. One patient does not make gene therapy predictable. Applicants point to the definitions of a “therapeutic effect” and an “anti-tumor effect” in the specification. The definitions call for at least a 10% amelioration of symptoms or tumor size. The specification does not provide adequate guidance to obtain at least 10% amelioration of a disease or tumor size. The examiner does not doubt the possibility of obtaining a therapeutic effect or anti-tumor effect using gene therapy. However, given the guidance provided in the specification taken with the unpredictability in the art, it would have required one of skill in the art undue experimentation to determine the parameters required to obtain a “therapeutic effect” or “anti-tumor effect” as claimed at the time the invention was made.

Applicants argue Verma et al. does not correlate to cancer treatment. Verma et al. correlates to cancer treatment in that it discusses the unpredictability in determining the vector required to obtain a therapeutic level of gene expression using gene therapy. Cancer is specifically mentioned on page 240, Table 1, 4th from the bottom and on page 241, column 2, the end of the second paragraph.

Applicants argue Alvarez-Vallina et al. of record (March 1, 1999, Human Gene Therapy, Vol. 10, pages 559-563; page 562, column 2, line 1) does not support unpredictability in how to use chimeric TCR to obtain a therapeutic effect. Applicants state that an admission that more is to be learned about TCR density in the T-cell response to antigen does not preclude therapy. Applicants state that the reference is unrelated to the instant invention because it does not teach

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the drug-regulatable system. Applicants arguments are not persuasive. The immunogenic polypeptide demonstrated in the specification is a chimeric T-cell receptor (TCR). The immunogenic polypeptide claimed encompasses a chimeric TCR given the example provided in the specification; therefore, the chimeric TCR of Alvarez-Vallina et al. correlates to the immunogenic polypeptide claimed. The specification does not teach the level of expression of a chimeric TCR required to obtain a therapeutic effect or an anti-tumor effect. Alvarez-Vallina et al. suggests that it was unpredictable what level of expression of a chimeric TCR would be required to obtain T-cell activation. Therefore, given the unpredictability in the art taken with the guidance in the specification it would have required one of skill undue experimentation to determine the parameters required to use a chimeric TCR to obtain a therapeutic or anti-tumor effect as claimed.

#### **Regulatory promoter systems**

The specification does not enable regulating gene expression using any drug-regulatable promoter as recited in parent claim 1 using any of the drugs listed in claim 10. Miller et al. of record (May 1, 1997, Human Gene Therapy, Vol. 8, pages 803-815) teach that it is unpredictable what cells the tetracycline system may be applied (page 809, column 2, 2nd full paragraph) and that the gene regulation system required to for successful gene therapy in humans is yet unknown (page 809, column 2, line 42). Miller et al. teach that attempts to produce regulatable systems for gene therapy based on inducible cellular promoters are fundamentally flawed because 1) the effects of the inducer must induce the endogenous promoter and the transgene promoter and 2)

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interference from endogenous activators may prevent expression (page 808, column 1, 2nd full paragraph). Applicants demonstrate transfecting T-cells with a chimeric TCR under the control of a tetracycline system and controlling expression *in vitro* (page 29) but do not correlate the results obtained to other drug-regulatable promoters, drug or cell line such that any drug-regulatable promoters, drug or cell line is enabled.

Applicants argue the system used by applicants addresses many of the drawbacks of the tet regulated system. The system used by applicants provides expression in a variety of cells lines. So did the tet system known in the art, although it may not be applicable to all cell lines (Miller et al. Page 809, column 2, 2nd full paragraph). The system used by applicants provides low gene expression and can be used to prevent toxicity. The claims merely require a regulatable promoter and are not limited to systems that provide low gene expression and can be used to prevent toxicity. The specification does not enable using glucocorticoid steroids, sex hormone steroids, LPS or IPTG (claim 10) because the specification does not teach the promoters that are controlled by these regulatory drugs (page 10, line 9). These promoters are considered to be essential to the practice of the invention for its claimed scope and have not been taught in the instant specification. The combination of promoter and drug is also essential to the invention and is not enabled as broadly claimed.

The specification does not enable regulating the expression of a polypeptide by altering the concentration of regulatory drug after the cell has been administered as encompassed by claim 1.

The specification does not teach dosage, routes of administration or methods of targeting cells

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transfected with the polypeptide such that expression can be regulated after the cells have been introduced.

**Other**

Claims 4-6 as newly amended are directed toward a method of regulating gene expression wherein the mammal has made an immune response to the immunogenic peptide prior to administration of the a cell. While page 22, lines 5-12 suggest such an approach, the specification does not provide a method to determine whether the mammal has made an immune response, circulating antibodies or immunocompetent memory cells which react with the immunogenic polypeptide as claimed. The specification does not teach how to regulate the expression of an immunogenic polypeptide in such a mammal or how to use such a method. The claims do not provide a nexus between a method of regulating a gene which results in an immune response. The preamble should reflect the substance of the claim.

Claims 7-9 are not enabled as written because there is no nexus between the preamble and body of the claims. Inhibition of the polypeptide *in vitro* as recited in claim 7 is not regulating the expression of a polypeptide in a mammal as in the preamble of claim 1. The specification does not enable regulating the expression of a protein in a mammal by regulating the gene while it is within the mammal.

The specification does not enable the term "delay interval" (claim 7). Applicants point out that the term is defined in the specification. Applicants argument is not persuasive. The phrase "a significant period, or a delay interval, (typically 2-10 days, preferably 4 days or longer)" does not

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define the term delay interval. It is unclear whether the phrase "2-10 days, preferably 4 days or longer" is the definition of delay interval or whether a delay interval is a period of time between a "significant period" and "2-10 days, preferably 4 days or longer". The method claimed requires a step of waiting for maximum gene expression. The definition of maximum gene expression is the highest level of expression obtained due to the presence or absence of a regulatory drug which can be any level of expression. Given the unpredictability in the art taken with the guidance provided in the specification it would require undue experimentation to determine the delay interval required to obtain a maximum level as claimed.

The specification does not enable using viral genome or viral vectors as in claim 13. Applicants argue viral vectors are mentioned in the specification (page 16, line 8) and known in the art and that it is not necessary for a patent disclosure to teach that which is known in the art. While viral vectors were known in the art and mentioned in the specification, given the unpredictability in the art regarding the vector used to obtain the desired result using gene therapy, the vector used is considered essential to the instant invention. Therefore, applicants have not enabled using viral genome or viral vectors to regulate gene expression in a mammal as claimed.

2. Claims 1-18 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 1 and 7 are indefinite because the phrase "regulating in a mammal the expression of a nucleic acid sequence" indicates that regulating the expression of a nucleic acid sequence occurs in the mammal; however, claim 7 states expression is inhibited *in vitro*. It is unclear whether applicants intend to regulate the expression in the mammal or *in vitro*.

Claims 4-6 remain indefinite because the preamble and the substance of the claims do not provide a nexus between the two. Applicants argue that the substance of the claim is not to make an immune response, induce circulating antibodies or immunocompetent memory cells. Applicants argument is not persuasive because the body of the claim results in making an immune response, inducing circulating antibodies or immunocompetent memory cells while the preamble is directed toward a method of regulating. Such a claim is confusing.

Claims 7-9 remain indefinite. Applicants argue the phrase "delay interval" is defined in the specification (page 9, line 17). The phrase "a significant period, or a delay interval, (typically 2-10 days, preferably 4 days or longer)" does not define the term delay interval. It is unclear whether the phrase "2-10 days, preferably 4 days or longer" is the definition of delay interval or whether a delay interval is a period of time between a "significant period" and "2-10 days, preferably 4 days or longer". The metes and bounds of the term cannot be determined.

Claim 9 remains indefinite because the phrase "substantial absence" is indefinite. Applicants argue the term is defined on page 5, line 7 as an amount or [sic] regulatory drug that does not stimulate an increase or decrease in the expression of an immunogenic polypeptide sequence that is operably linked to a promoter that is regulated by this same regulatory drug. The

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definition relates to the amount of drug that does not alter gene expression, but does not teach what applicants consider significant or what immunological or enzymatic methods are used to determine gene expression. The definition does not provide adequate information to determine the metes and bounds of how substantial the absence is.

Claim 14 as amended is indefinite. It is unclear what the phrase "in a mammal" refers to and whether applicants intend to claim a cell in a mammal, altering the drug in a mammal or controlling expression of a gene in a mammal.

***Claim Rejections - 35 USC § 102***

3. Claims 14-17 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Taichman et al. (1993, Biotechniques, Vol. 14, pages 180 and 182) for reasons of record.

Taichman et al. teach an isolated T-cell transfected with a plasmid encoding a tyrosine kinase operatively linked to an inducible MT-I promoter which is controlled by altering the concentration of zinc in the media (page 180, column 2, line 13; page 180, column 1, second to last sentence). The tyrosine kinase protein is equivalent to the "immunogenic polypeptide" because it is immunogenic. The media taught by Taichman et al. is equivalent to the physiologically acceptable diluent claimed. Applicants argue that Taichman et al. do not teach controlling the expression of the polypeptide in a mammal. The phrase "may be controlled by altering the ... drug to which the cell is exposed in a mammal" is an intended use and may not occur. The phrase does not bear patentable weight when considering the art.

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***Conclusion***

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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